REMARKS

Claims 21-25 remain in this application. No amendments have been made herein.

The Objections

Claim 21 was objected to (at line 8) for alleging reciting "an a". Applicants have reviewed the previous Amendment; "an" was lined through, and it is believed that the claim was correct as presented.

Withdrawal of Certain Prior Art Rejections

Claim 25 is now deemed free of the prior art. The 35 U.S.C. 102(b) rejections of claims 21, 22 and 24 have been withdrawn.

The Rejections under 35 U.S.C. 103

Claims 21-24 have been rejected under 35 U.S.C. 103 as allegedly unpatentable over Takao *et al.* (1996) in view of Ford *et al.* Applicants respectfully traverse this rejection.

Based on the Examiner's discussion and the inconsistency in the Office Action, it is believed that this rejection was meant to be made under 35 U.S.C. 103 and not 102(b). Applicants have responded as if the rejection were made under Section 103 rather than 102(b). A supplemental response will be provided if this understanding is incorrect.

The methods of claims 21-24 relate to UV damage endonuclease proteins which are truncated, stable, and are capable of effecting enzymatic activity related to DNA damage repair. Claims 21 and 23 were amended to recite SEQ ID NO:6 (the GST tail fused to the truncated UVDE protein). Importantly, and surprisingly, the truncated Uve1p proteins or Uve1p fusion proteins of the present invention are stable upon purification and retain enzymatic activity when substantially purified, especially to 90% or greater purity, thus

insuring utility of these proteins in DNA repair. The cited Takao reference does not enable the methods of claims 21-24 because this reference does not teach a truncated Uve1p protein which exhibits stability and high enzymatic activity in a substantially purified state (90% or greater), nor does this reference teach fusion proteins. Rather, the cited reference teaches away from the possibility obtaining a stable truncated Uve1p that could be used in methods for cleaving distorted DNA, as claimed.

A careful reading of the Takao reference reveals that this reference teaches that the truncated endonuclease was not stable in pure form, and that the assays described therein were carried out with endonuclease preparations which were only about 35% pure (page 1269, column 1). By contrast, the present application teaches that the truncated UVDE proteins were purified to nearly electrophoretic homogeneity and that the proteins made were stable in pure form. The cited reference does not teach a GST-truncated UVDE fusion protein (SEQ ID NO:6), as recited in claims 21 and 23. Claim 21 specifies that the truncated endonuclease based on SEQ ID NO:4 is purified. Thus, Applicants respectfully submit that the present claimed invention is effectively distinguished over the teachings of the cited Takao reference. The purified endonuclease preparations of the prior art were not stable, as are those taught in the present application. Moreover, the cited reference does not each endonuclease activity on all the types of distorted DNAs as taught in the present case, nor does this reference provide for a reasonable probability of success in the claimed methods, as required by In re O'Farrell, 7 U.S.P.Q.2D 1673, C.A.F.C. 1988.

Claims 21 and 23 recite the use of the endonuclease consisting of the amino acid sequence of SEQ ID NO:6 (GST-truncated Uvelp) for action on UV-irradiated DNA and DNA containing photoproducts causing distortion. SEQ ID NO:6 is not taught by the cited reference. In addition, claims 21 and 22 as amended recite SEQ ID NO:4, the truncated UVe1p in stable, purified form (at least 90%). As noted, the reference does not disclose a stable, purified, truncated enzyme.

The Takao reference does teach a truncated enzyme prepared from recombinant *E. coli*, although it is said not to be stable in purified form. It does not teach that the instability is a result of the expression host or that stability would be improved in a different recombinant host. The Takao reference does not enable a stable purified truncated UVDE enzyme.

The shortcomings of the Takao reference have been discussed previously in the prosecution of this application and have been repeated herein. The Takao reference did not teach or suggest that a stable, purified truncated UVeP1 could be prepared. There is no teaching or suggestion that the recombinant host cell was the source of the instability, as the Patent Office appears to have theorized. Applicants circumvented the problems inherent in the Takao reference and have provided to the art a truncated UVeP1 which is stable as an active protein in purified form.

With respect to the mention at page 1271, right column, line 20, of expression of the referenced gene in *Saccharomyces*, Applicants respectfully maintain on the record that there is no indication that this expressed gene product was purified from the *Saccharomyces* host cell. The context of the paragraph suggests to the undersigned that complementation studies in *Saccharomyces* were carried out. Such complementation studies typically involve intact (live) cells and **not** purified proteins or even cell-free extracts.

The Patent Office has acknowledged that difficulties in preparing a purified enzyme were reported by Takao. The Patent Office has characterized the cited Ford reference as teaching a fusion protein comprising a GST tail fused to an enzyme of interest. The Patent Office has concluded that it would have been obvious to one of ordinary skill in the art to "have the method of Takao *et al.* and to modify the expression and purification of the UVDE endonuclease as taught by Ford."

The modification is said to come from the Ford reference which states "On a lab scale fusion tail recovery systems are powerful and elegant tools to one-step recovery and purification of recombinant proteins or identification of proteins encoded by cloned cDNAs. On an industrial scale, fusion tail technology can be used in the recovery and purification of both higher-cost pharmaceuticals and lower-to medium-cost enzymes." The Patent Office has alleged that the expectation of success is high because of well-developed and routine use of the GST fusion protein in the art.

Applicants respectfully remind the Patent Office that where references are combined, the motivation for their combination must come from the references themselves. The cited Takao reference does not state the origin of the instability of the truncated enzyme -- was it a destructive activity in the recombinant cell extract or was it an inherent property of the truncated enzyme protein? Although the Ford reference states that the GST tail has been used to produce a large number of intracellular target proteins, there is no teaching or suggestion in either of the cited references to combine the GST tail with the truncated UVDE protein to allow purification of the truncated UVDE such that it is stable in purified form. Applicants respectfully note that the Ford reference provides 8 types of tails, including 3 different enzyme-based tails, which had been used in recombinant protein production. Where the truncated UVDE was taught by Takao to be problematic as a purified enzyme, it could not have been more than obvious to try a fusion protein approach to remedy the instability. There is nothing that suggests that this approach, specifically the GST approach, would allow the purification of a truncated UVDE that is stable. Obvious to try is not the proper standard for a conclusion of obviousness (In re O'Farrell, 7 U.S.P.Q.2d, 1673, C.A.F.C, 1988).

In view of the foregoing discussion, Applicants respectfully maintain that the cited references do not render obvious the invention as claimed, and that the rejection must be withdrawn.

The Rejections under 35 U.S.C. 112, first paragraph

Claims 21-24 have been rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the Specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the invention at the time the application was filed. Applicants respectfully traverse this rejection.

The Patent Office has states that the claims are directed to a method for cleaving double stranded NDA with certain DNA lesions: platinum diadduct, intercalating molecule, alkylation of nucleotide. It has been alleged that neither the subgenera of lesions nor the specific activity of the *S. pombe* truncated UVDE are sufficiently described. It is alleged that only one platinum diadduct is shown and that activity against others Is not shown. The disclosure is alleged to be silent as to any intercalating molecule, which when intercalated, is recognized by the truncated UVDE. The disclosure is alleged to be silent as to any alkylation of a nucleotide which is recognized by the truncated UVDE.

Applicants respectfully maintain that the application and claims state that the enzyme has the noted recognition. This constitutes written description. Applicants invite the Examiner to cite the relevant section of the Statute which requires specific exemplification and data related to every aspect of a claimed invention.

Claim 25 has been rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the Specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the invention at the time the application was filed. Applicants respectfully traverse this rejection.

The Patent Office has alleged that the claims is directed to methods using certain DNA cleavage enzymes and relating to certain DNA lesions. It has been alleged that there is a "complete lack of written description".

Applicants respectfully maintain that the description and claims state that the enzymes have the noted recognition. This constitutes written description. Applicants invite the Examiner to cite the relevant section of the Statute which requires specific exemplification and data related to every aspect of a claimed invention.

Claims 21-25 have been rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the Specification in such a way as to enable one skilled in the art to make and use the invention. Applicants respectfully traverse this rejection.

The Patent Office has alleged that the Specification fails to teach DNA lesions related to alkylation or intercalation and that undue experimentation would be required to make and use the invention. Applicants respectfully disagree. The level of skill in the relevant art is very high. Applicants have taught excision assays using a variety of distorted DNA substrates. For the skilled artisan it would be straightforward to verify the excision activity of an enzyme taught by present applications in an assay analogous to those specifically exemplified in the application but using another substrate of interest. The commonality of substrates of the present enzymes is distortion of the double stranded DNA structure. The Specification teaches cleavage of DNA substrates distorted by a variety of agents or damage. Thus, it has been concluded that the distortion is what the enzyme(s) recognize(s), not a particular type of damage. The Examiner has not provided any cited references to support the conclusory statements that the unpredictability of specificity toward a particular substrate is high or that the probability of success is low. If the Examiner is aware of evidence on which to base a different conclusion, she is invited to

bring that to Applicants' attention and place it on the record. No undue experimentation would be required. Applicants have stated that the enzymes have the noted activities.

The Patent Office has not provided sound scientific reasoning, references or Examiner's affidavit to doubt that adducts other than the particular GG platinum diadduct specifically exemplified would not be referenced by the enzymes set forth in the claims. With respect to intercalating molecules, Applicants have, at page 7, lines 13-15, of the Specification, have referred to acridines and ethidium halides.

The Patent Office has alleged that the disclosure is silent with respect to any alkylation of a nucleotide that is recognized by the DNA repair enzymes set forth in the claims.

Applicants respectfully maintain that this is abundantly clear to the art, and where the double stranded DNA structure is distorted by alkylation of a nucleotide such that there mismatch, there will be excision. No undue experimentation is required on the part of the ordinary skilled artisan, who is of relatively high skill and technical sophistication.

The Patent Office has provided no sound scientific reasoning, affidavit of the Examiner or cited reference(s) to provide the basis to doubt assertions by Applicants, as is required by the courts (see, e.g., In re Marzocchi, 169 U.S.P.Q. 367, C.C.P.A., 1971). Neither is undue experimentation required to confirm the activities of the enzymes noted in the claims. Applicants' contribution to the art is the recognition that distortions in the double stranded DNA are recognized by certain DNA repair enzymes, especially the truncated and stable Uve1p, where the distortion is relatively nonbulky. While all claimed distortions are not experimentally described, Applicants have understood the characteristic nature of the enzyme substrate and they are entitled to breadth of claims in accordance

with their contribution to the art. Practice of the invention claimed will not require undue experimentation.

In view of the foregoing, the rejection is not proper and the rejection must be withdrawn.

Allowable Subject Matter

The Examiner has indicated willingness to allow claims to activities of the endonuclease of SEQ ID NO:4 or NO:6 in methods of cleavage of a double-stranded NDA containing the certain lesions: Dewar isomer of 6-4 photoproduct, abasic site, uracil, dihydrouracil, platinum-DNA GG diadduct, mismatched nucleotide and loop of less than 5 nucleotides.

Conclusion

In view of the foregoing, it is submitted that this case is in condition for allowance, and passage to issuance is respectfully requested.

If there are any outstanding issues related to patentability, the courtesy of a telephone interview is requested, and the Examiner is invited to call to arrange a mutually convenient time.

This Amendment is accompanied by a Petition for Extension of Time (two months) and a check in the amount of $210.00 as required by 37 C.F.R. 1.17(a)(2) to Deposit Account No. 07-1969. It is believed that this amendment does not necessitate the

payment of any additional fees under 37 C.F.R. 1.16-1.17. If the amount authorized is incorrect, however, please charge the correct amount to Deposit Account No. 07-1969.

Respectfully submitted,

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